Remarks

Claims 43-45, 47, 51, and 59 were pending in the application, and subject to non-final rejection. By this amendment, claims 43, 47, and 59 have been amended, and new claims 60 and 61 have been added. After entry of this amendment, **claims 43-45, 47, 51, and 59-61 are pending.**

No new matter is added by the amendments made herein.

The invention and outstanding rejections

35 USC 103

The pending claims were rejected by the Examiner for obviousness (35 USC 103).

MPEP 2141 sets out the basic considerations applying to obviousness rejections. These are:

(a) the claimed invention must be considered as a whole;
(b) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention;
(d) reasonable expectation of success is the standard with which obviousness is determined.

Furthermore, MPEP 2142 confirms that a *prima facie* case of obviousness requires three basic considerations:

(i) suggestion or motivation, in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
(ii) a reasonable expectation of success;
(iii) the prior art references must teach or suggest all the claim limitations.

The invention considered as a whole

Claim 43 relates to treatment of metastatic tumors occurring in, but not originating in, the central nervous system (CNS), that is treatment of CNS secondary tumors derived from primary tumor cells not of the CNS.

The treatment method involves injection of an avirulent HSV-1 consisting of an HSV-1 genome modified with respect to the wild type by a modification to the HSV-1 genome wherein the modification consists of a mutation in the γ34.5 gene. The claim language has been carefully formulated, including discussion with the Examiner at interview, to clearly indicate the extent of modification to the genome.

The virus is effective in that it replicates within the tumor cells and results in lysis of those cells. Moreover, to be effective in this treatment the virus must exhibit selectivity in that non-tumor CNS cells surrounding the tumor are not lysed.

So one could see the invention as a whole in finding that an HSV-1 modified in the recited manner is useful to selectively treat metastatic (secondary) tumors occurring in the CNS, but without causing detrimental damage to the surrounding healthy tissue.

Amendment to the claims

Claim 47 has been amended to correct an obvious typographical error. Minor amendment has been made to previous claims 43 and 59 to indicate that the treatment method involves lysis of the tumor cells, not just infection and replication. Lysis is discussed throughout the disclosure, for examples please refer to page 18, Example 1, page 34, Example 36 and page 38, penultimate complete sentence.

New independent claims 60 and 61 are submitted corresponding to independent claims 43 and 59 respectively wherein the HSV is limited to HSV1716.

Relevant facts

An understanding of certain scientific issues is important in understanding the present invention and the teachings of the prior art.

To assist the Examiner, Applicants submit herewith a Declaration (pursuant to 37 C.F.R. §1.132) by inventor Susanne Moira Brown, Ph.D., in respect of the topics of primary and

secondary tumors and replication and virulence in HSV. The following comments are made in conjunction with that declaration.

Replication and virulence

It is important for the Examiner to understand that in herpes simplex virus (HSV) there is a distinction between replication and virulence.

Virulence is connected with cell death, and is usually used to describe virus induced cell death in the body, *i.e. in vivo*. Replication is concerned with viral reproduction. Replication of HSV *in vivo* can take place by one of two modes – the first is lytic replication where the newly formed HSV lyse the infected cell. Cell death ensues and one may be able to say that the virus is virulent in that cell type under the relevant conditions of the experiment. The second mode is latent replication. HSV infects over 80% of the world's population and for many of us, the infection is predominantly latent. In this form, viral replication is occurring, but the spread of virus from one cell to another does not involve cell lysis. A virus which infects in a latent manner is unlikely to be virulent.

The Examiner will therefore understand that ability to replicate does not equate with ability to lyse and that replication does not directly correspond with virulence.

It is asserted that HSV1716 "is capable of killing non-neuronal tumor cells via oncolysis since it still retains the ability to replicate in the peripheral tissues" (page 6 of the Office action under response). This is incorrect for two reasons. Firstly, replication is not equivalent to virulence or lysis as explained above.

Secondly, *in vivo* lytic replication is not necessarily occurring. For a given HSV, its behavior *in vitro* is not a direct indicator of its behavior *in vivo*. The balance between latent and lytic replication cycles can be upset *in vitro* where extracellular conditions are relatively abnormal and can drive the HSV into a lytic state. Indeed, experiments to determine replication kinetics, normally performed *in vitro*, are designed to encourage a lytic mode of replication as

this permits the formation of plaques, which is the measure ('plaque forming unit' (pfu)) used to determine replication.

To support this, Applicants submit herewith (in an Information Disclosure Statement) a copy of 'Intralesional injection of herpes simplex virus 1716 in metastatic melanoma' Rona M Mackie, Barry Stewart and S. Moira Brown, *The Lancet* Vol. 357 February 17, 2001 (referred to herein as Mackie). This paper relates to trials of HSV1716 in human patients, more specifically in patients with metastatic melanoma. The paper confirms that *in vitro* HSV1716 replicates as efficiently as wild-type virus in actively dividing cells and "replicates preferentially in human melanoma cell lines *in vitro*, causing cell lysis and death" (page 525 col. 1). Moreover, on page 526 col. 1 the authors indicate that:

> "Immunohistochemical staining of sections from virus-injected and saline injected nodules [of patients *in vivo*] showed that HSV antigen was confined to the melanoma cells in virus-injected nodules only with no evidence of virus antigen in normal cells and specifically non in the basal layer of the epidermis. This finding is encouraging in light of reports from animal studies that the metabolically active cells of this layer such as basal layer keratinocytes, and also normal melanocytes might support HSV1716 replication."

HSV1716 does not replicate promiscuously in the peripheral tissues, the Mackie paper confirms at least this, and in those peripheral tissues where replication may occur this does not equate with lysis or virulence.

In this regard, it is noted that statements at page 4 and 6 of the Office action are inconsistent. At page 4, the Examiner indicates that 1716 has an ability to replicate in the peripheral tissues. This is not disputed, but it should be remembered that this replication is not necessarily lytic. At page 6, the Examiner says that the genetically altered viruses sought in Martuza (col. 1-2 bridging paragraph) are not capable of replication in non-dividing cells to avoid systemic infection. This highlights the suggestion in Martuza that viruses which are non-replication competent in non-dividing cells are required, but then combines that teaching with the ability of 1716 to replicate in peripheral, and in most cases non-dividing, tissues.

The important point is that replication and virulence can be connected in some circumstances, but that **replication is not equivalent to and does not always lead to lysis**. As such, information about replication of a given HSV in certain tissues does not in itself indicate whether or not one can expect that virus to be virulent for that cell type.

Primary and secondary tumors

Primary and secondary tumors represent distinct neoplastic tissue and can be distinguished by different biochemistry, morphology, genetic markers and responsiveness to treatment. Many therapeutic strategies focus on the treatment of primary tumors, and it is not uncommon to find that the primary tumor is treated with some degree of success only to find that a secondary tumor, derived from the primary tumor but occurring in an unrelated tissue, develops which is unresponsive to the treatment successfully employed for the primary tumor.

It follows that no assumptions as to the degree of success which can be obtained in the treatment of secondary tumors can be made from the treatment of a primary tumor with the same therapeutic, even where the secondary tumor is considered to be derived from the primary tumor concerned.

<u>The cited references considered as a whole</u>

US 6,139,834 (Martuza)

Martuza relates to a herpes simplex virus vector altered in two ways – (i) in the γ34.5 gene; and (ii) in the ribonucleotide reductase gene. For example, see claim 1 and col. 1 line 16:

> "...the present invention relates to a mutated, replication-competent Herpes Simplex virus-1 (HSV-1) which contains mutations in two genes...".

These two features are present throughout the disclosure and are essential features of Martuza. Any teaching afforded to the skilled person by Martuza must recognize that the result in Martuza is attributable to this combination of mutations. The contribution of each mutation to the properties of the disclosed mutant virus is not separable. The disclosure is only enabled in as

far as the teaching of the document extends and that teaching is clearly limited to a virus having two mutations, the contribution of each mutation to the result not being individually assessed or disclosed.

Martuza only describes killing of **primary** tumor cells. Claim 3 and col. 3 list many tumor types (most of which are speculative). Regardless of the speculation, all tumor types listed relate to primary tumors cells and the description and context of Martuza does not indicate otherwise. This is an important point. At page 7, 2nd paragraph, the Examiner indicates that melanoma reads onto intracranial metastases. This is incorrect. Melanoma is a specific primary tumor of, and occurring in, the skin. Reference to melanoma cannot, unless clearly indicated, extend to those other tumors which may be derived from the melanoma.

Martuza only describes one experiment in which tumor cells are treated. This is Example 3 and considers an *in vivo* extracranial model comprising a glioma (primary brain tumor) xenograft. Examples 4-8 are all speculative and were not performed. As such there are no results for these experiments and the patent teaches nothing in this respect regarding the efficacy of the disclosed virus in intracranial models. In any event, any teaching would of course be directly connected to the presence of a modified ribonucleotide reductase gene in the virus.

WO 92/13943 (Brown)

Brown relates to HSV-1 variants which are modified to lack neurovirulence. The variant HSV 1716 is disclosed.

The disclosure relates to the property of non-neurovirulence of certain variants of HSV Glasgow strain 17^+. This is assessed by intracranial injection of virus into mouse brain followed by determination of the LD_{50}, that is, how much virus is required to kill 50% of the mice tested.

The results show that certain variants can be considered to lack neurovirulence owing to the fact that the LD_{50} value is very high, *e.g.* $>10^6$. The lack of neurovirulence is attributable to modifications to the genome in the Bam HI s region in the internal and terminal repeat (TR_L and IR_L) regions of the genome.

The Examiner refers at page 4 of the Office action to non-neurovirulence being attributable to a replication defect in the CNS environment. In this case, non-neurovirulence may well be attributable to lack of replication, but this is not an inevitable cause and effect pathway as HSV can have two modes of replication. One is a lytic replication cycle in which viral DNA is replicated and packaged within the cell and lysis follows in order to infect neighboring cells – this will most likely cause the virus to be virulent as cell death necessarily occurs on lysis. The other mode is a latent replication cycle in which the virus is replicated and packaged, but infection of neighboring cells is not the result of lysis, viral particles being transported from the cell in a non-lytic manner. Thus **ability to replicate is not equivalent to virulence**.

Brown is not concerned with tumors or tumor cells, nor with their treatment or their lysis. The teaching is that of lack of neurovirulence, *i.e.* avirulence in neuronal cells, which, if there is any teaching in connection with lysis of cells by modified HSV, is a teaching of the property of lack of lytic ability in the CNS for the particular strain 17 variants described.

The disclosure as a whole informs the skilled person that certain HSV-1 strain 17 variants lack neurovirulence and that this neurovirulence is attributable to modifications made in particular regions of the genome.

MacLean et al

This paper is the publication corresponding to the Brown patent application (WO 92/13943). Accordingly, it describes the construction of certain variants of HSV-1 strain 17, including the variants 1716 and 1714, and discloses the non-neurovirulence of these variants.

The Examiner refers at page 5 to the replication of HSV1714 in a wide variety of rapidly dividing cells *in vitro* (Table 2 on page 635 refers which is also disclosed in Brown). The experiments performed were in respect of HSV1714 and were aimed at determining whether the virus was host-restricted. The Examiner points out that replication occurred in a wide variety of cell types, including the HFL cell line. This is not an erythroleukemia cell line but is in fact

human fetal lung, *i.e.* not tumor cells. One can also point out that replication occurred in BHCK, Vero and 3T6 cells, which are also non-tumor cell types. Thus, all one can say from this experiment is that HSV1714 is capable of replication in several cell types under *in vitro* conditions. *In vitro* replication experiments are usually performed under conditions which force the HSV through a lytic replication cycle, in order that plaque forming units (pfu) can be used as the measure of replication. However, this gives no information as to the type of replication cycle which would occur *in vivo* – it may be latent or lytic. Moreover, as replication occurred in several cell types, these results do not indicate any selectivity of HSV1714 for either replication or lysis between cell types.

Bolovan et al

Bolovan is concerned with the attenuated neurovirulence of certain HSV-1 strain 17 mutants wherein specific mutation is made in the ICP34.5 gene. It is not concerned with the treatment of tumors, of any kind.

Three mutant viruses were created and investigated. Mutant 17del8A contained a deletion of eight codons in both copies of the ICP34.5 gene. Mutant 17termA was the result of insertion of a 20bp linker sequence into the *Bst*EII site within the *Bam*HI S+Q fragment. Viral isolates containing the mutation in both copies of the ICP34.5 gene were identified. The linker inserted was the same as that used to generate mutant R4009 in strain F and was predicted to result in premature termination of the ICP34.5 protein after the initial 30 amino acids. The third mutant was a restored virus 17termAR in which the insertion was removed from 17termA by cotransfection with wild type 17+ *Bam*HI S+Q sequence.

Thus, the mutants created and investigated were part of a follow up to the work in Brown and MacLean, but in this work the ICP34.5 gene, which by this time had been characterized in strain 17, was specifically targeted for mutation by the use of a deletion or insertion.

The experiments centre on the neurovirulence, or lack of neurovirulence, of the mutants. PFU/LD_{50} ratios were investigated in intracranially inoculated mice. A contrast was noted between the 100,000-fold reduction in neurovirulence reported for a premature termination

mutant of ICP34.5 in strain F and a 25- 90-fold increase in the PFU/LD_{50} ratio for the mutants under investigation (page 51, col. 2, 2nd paragraph and Table 1). The authors could not provide a reason for the difference in neurovirulence phenotype (pages 51-52, bridging text and page 54 2nd full paragraph)), but it was not attributable to contamination with wild-type virus (page 52 col. 1 first paragraph). It appears that the mutants created by Bolovan *et al.* were not completely avirulent, at least as far as the CNS tissues are concerned, *i.e.* when intracranial inoculation was used (in contrast to footpad inoculation of the peripheral tissues). Indeed, the authors conclude that:

> "...clearly this gene does not play as predominant a role [in neurovirulence] in strain 17syn+ as was suggested for strain F" (page 53 'Discussion' col. 2 end of first paragraph); and
>
> "It therefore seems likely that the neurovirulence displayed by ICP34.5 mutants is the result of a combination of factors and depends on the genetic background in which the mutation is expressed" (page 54 col. 1 end of 2nd full paragraph).

The authors point to the importance of the physiological state of the cell in overcoming the restriction of replication of ICP34.5 mutants (page 53 col. 2, before 'Discussion') as well as the genetic background of the cells infected with the virus (page 54 col. 1 2nd full paragraph, last sentence). In seeking an explanation for this result the authors hypothesize that factors may be present in actively dividing cells to complement the ICP34.5 termination mutant (page 54 col. 2). Tests were performed *in vitro* in MEC (mouse embryo cells) under confluent (largely quiescent) and subconfluent (actively dividing) conditions. The authors consider that the results:

> "... suggest a function is present in actively dividing MEC which is able to compensate, at least partially, for the replication restriction seen with this mutant [17termA] within confluent primary MEC cultures" (page 52 col. 1).

These results must be taken in context, indeed to do so is necessary if the document is to be considered as a whole. The experiments performed are *in vitro* experiments and are performed in mouse embryo cells. Clearly, a metastatic tumor occurring *in vivo* in the CNS, comprising a mass of complex neoplastic cells uncommon to the CNS and surrounded by healthy neural cells are distinct from a culture of mouse embryo cells.

Furthermore, the distinction between actively dividing and non-dividing cells used in the authors' experiment is crude and a result of laboratory created conditions. The experiments only permit conclusions in as far as the procedures extend. In this case, they only provide conclusions in respect of the behavior of the particular HSV mutants tested in mouse embryo cells ***in vitro***. This is a long way from providing an indication of how similar mutants would act in metastatic tumor cells in the CNS *in vivo*.

This appears to be recognized by the authors who indicate that "further experimentation" is required (page 54 col. 2, first paragraph). In itself, this statement summarizes the provisional nature of these results and emphasizes that further research is required because the situation *in vivo* is uncertain and not predictable.

US 6,340,673 (Roizman)

Roizman does not teach the treatment of a metastatic tumor occurring in the CNS.

Applicant is aware that the Examiner will consider the patent enabled across the scope of the claims. In determining that scope, the claims must be construed in conjunction with the description, which, in as far as the application relates to treatment of tumors only discusses **primary neuronal** tumors, usually neuroblastoma cells ***in vitro***.[1] The term neuronal tumor is indicative of the origin of the tumor, *i.e.* neuronal cells, and the cells tested are primary tumor cells. In any event, the application does not mention, or suggest, that the claimed viruses can be

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[1] In this respect careful consideration of the examples in Roizman is a useful exercise:

- Example 1 – this relates to impact on programmed cell death and is performed *in vitro* in Vero cells and SK-N-SH neuroblastoma cells;
- Example 2 is speculative and does not appear to have been performed, and in any event refers to gene therapy;
- Example 3 relates to methods of introduction of the γ34.5 gene to the CNS by the use of cell lines passaged *in vitro*.
- Example 4 relates to treatment of cells by the protein expressed by the γ34.5 gene;
- Example 5 is concerned with screening for substances that mimic the function of γ34.5 to prevent neurodegeneration. The experiments are all performed *in vitro* in neuroblastoma or Vero cells;
- Example 6 mentions induction of cell death in tumor cells, but is concerned with screening for substances which trigger cell death in tumor cells. Again, the experiments are perfomed *in vitro* using specific cell lines.

There are no experimental teachings in Roizman regarding the treatment of tumors *in vivo*.

used to treat metastatic (secondary) tumors of any kind. The Examiner appears to agree with this analysis on page 9 of the Office action.

The Examiner also refers to the statement at col. 18 before Example 1 referring to the proposed function of the γ34.5 gene product. The results are couched in terms of cellular protein synthesis, which per se and without further explanation, are unclear. Reference is made at the end of the statement to production of infectious progeny and presumably the inventors are referring to the replication characteristics of the mutants in neuronal and non-neuronal cells. If this is true, the implication is that replication in neuronal cells requires a functional γ34.5 gene product, but replication in non-neuronal cells does not.

However, **replication and virulence must not be confused**. For example, in Bolovan the 17termA mutant replicated with kinetics indistinguishable from that of the wild type strain 17syn$^+$, but were completely avirulent when inoculated on either the footpad or the eye (see page 52 col. 1). This is because HSV permits non-lytic replication as well as lytic replication. Virulence is generally associated with the latter; a latent infection may involve the former.

Lysis (cell destruction) is required for an effective therapeutic treatment of the tumor. From Roizman, it is not possible to conclude or reasonably expect that infection of non-neuronal cells with a mutant having a non-functional γ34.5 gene will result in **lysis** of the cells, although replication may occur.

Roizman does not discuss lysis. Claim 1 of Roizman describes 'suppression of growth of the tumor', which is not entirely clear but seems to indicate that a halt or reduction in tumor growth takes place. This is in agreement with the description. For example, col. 18 lines 9-15 discuss shut-off or sustained protein synthesis in connection with virus replication ('production of infectious progeny'). Col. 5-6 indicates that the "..."γ34.5 minus" virus can induce apoptosis and thereby cause death of the host cell, but this virus cannot replicate and spread...." So, according to Roizman, the process of tumor treatment of infection, replication and lysis (forming part of the claims of the present application) does not occur, rather induction of apoptosis is proposed (*e.g.* see col. 5 line s 66-67 and/or col. 25 lines 35-39).

Taken as a whole, Roizman tells the skilled person that an HSV-1 mutant lacking an expressible γ34.5 gene can be used to treat **primary neuronal** tumor cells ***in vitro***. It also indicates that replication in neuronal cells may require a functional γ34.5 gene product.

However, Roizman does not inform the skilled reader of the relationship between absence of a γ34.5 gene and lysis of non-neuronal tumor cells in a neuronal background (the CNS). Indeed starting from Roizman, one may expect protein synthesis shut-off and lack of virus replication of cells in the neuronal environment (col. 18 lines 10-13).

Amer et al

This paper describes the result of a study of 122 patients with advanced cutaneous malignant melanoma. That is, patients with primary melanoma. The paper is mainly concerned with the prediction and confirmation of the existence of intracranial metastases by electroencephalography (EEG).

The occurrence of metastasis of the primary melanoma to the CNS, liver and lung is confirmed. The CNS metastases being secondary (metastatic) melanomas.

The paper also confirms the seriousness of CNS metastases:

"Mean survival after neurological diagnosis was 4.0 months, ..." (abstract)

"Once the patient becomes symptomatic, death usually ensues in a few months;..." (page 660 col. 2).

Available therapeutic strategies are discussed at page 663 col. 2 and on page 666 col. 2. Surgical resection is considered to offer patients the greatest chance of survival.

When considered as a whole, Amer does little more than confirm to the skilled reader the existence of primary melanoma derived CNS metastases and highlight the severity of the condition and lack of satisfactory treatments.

Budman et al

Budman further highlights the difference between a primary melanoma and a CNS metastatic (secondary) tumor which may be derived from a primary melanoma. The 'metastatic' nature of the CNS tumors is referred to throughout, *e.g.* see page 327 top and middle of col. 2, page 328 col. 2, page 329 bottom of col. 1 and col. 2 start of last paragraph.

Budman confirms that one of the most common forms of death in the patients studied, which all had 'biopsy-proven malignant melanoma' (abstract) was a CNS involvement (page 328 top of col. 2).

Budman also indicates that the CNS involvement also usually involves 'multiple mass lesions in the brain'. This emphasizes one of the morphological distinctions which can be made between primary and secondary tumors.

Budman can be considered as a similar teaching to Amer. It confirms the existence of CNS metastatic tumors derived from primary melanoma and their clinical significance.

Olofsson et al

The teaching of Olofsson does not appear to add anything in particular. The Examiner indicates that Olofsson teaches HSV-1 to **infect** metastatic melanoma cells. In fact, Olofsson refers to infection of B16 mouse melanoma cells, which have a "massive metastasizing potential". That is, the B16 cells are **primary** melanoma cells.

It is important to note that infection, replication and lysis are not equivalent or necessarily the inevitable result of each other and the teaching of Olofsson is limited to infection.

Given the fact that the molecular characteristics of a secondary tumor may differ significantly from the primary tumor from which it is derived, the teaching of Olofsson is in fact narrow and is limited to the infection of primary melanoma cells with HSV-1 strain F.

Combinations made in the Office action

The Office action refers to several combinations of documents to raise the obviousness objection. Each combination is discussed below.

Martuza and Brown

If the teaching of Martuza and Brown is combined the skilled person is lead to introduce an alteration to the ribonucleotide reductase gene. This is inescapable because it is the teaching of Martuza. The skilled person would not select particular aspects of Martuza to combine with Brown. To take this approach is to use hindsight, which of course is impermissible.

The Examiner indicates that Martuza specifically teaches that viruses have been tested in the prior art for their ability to treat various types of tumors and that genetic alteration so that the virus is not capable of replication in non-dividing cells is important (col. 1 line 44 to col. 2 line 5 is cited). There are several problems with the combination of this statement and the teachings of Brown:

(i) Ability to replicate does not directly equate with ability to lyse cells (discussed above).

The Examiner says that HSV1716 replicates in peripheral tissues – many of which will be non-dividing cells. Yet Martuza is looking for viruses which do not replicate in non-dividing cells.

It is untrue to say that Brown teaches lysis of non-neuronal tumor cells because it retains an ability to replicate in the peripheral tissues. This is going beyond the content of Brown and is assuming that replication is inevitably followed by lysis. There is in fact some uncertainty in predicting whether HSV1716 will replicate in a given peripheral tissue. In the event that it does this may well be a latent infection – indeed most HSV infections are predominantly latent.

(ii) Brown is concerned with lack of neurovirulence. The teaching is that HSV1716 is non-neurovirulent in (*i.e.* does not lyse) **non-tumor** neuronal cells. Brown is not concerned with lysis of tumor cells.

One cannot look at Martuza and see that a common factor between the virus of Martuza and that in Brown is a modification to the γ34.5 gene and thereby reach the present invention because it is not possible in Martuza to separate the contribution to the γ34.5 gene modification from the ribonucleotide reductase gene modification. Brown does not disclose the required information about lysis of tumor cells to do this. To make this conceptual leap of thought is to do so with hindsight.

However one chooses to combine the teachings of Brown and Martuza, the information disclosed in Brown and Martuza simply does not allow one to reach the presently claimed invention.

Roizman and Brown

The Examiner states at page 9 of the Office action that HSV-1 mutant 1716 and R3616 "... had been taught by the prior art to be effective for the same purpose, that is oncolysis of tumor cells". In respect of HSV1716, the prior art referred to is not mentioned. Of the prior art cited Brown and MacLean relate to HSV1716, and both refer to the same experimental work. However, neither document refers to HSV1716 as being effective for the purpose of oncolysis of tumor cells. It is true that Brown and Maclean teach non-virulence to cells of the CNS (*i.e.* non-neurovirulence), but that is the extent of the teaching, it does not extend to oncolysis.

It is stated at page 9 of the Office action that:

"It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the disclosed construct of WO 92/13943, HSV-1 mutant 1716 for the R3616 non-neurovirulent HSV-1 mutant of US Patent No. 6,340,674 in the method of US Patent No. 6,340,673 <u>because each of these agents had been taught</u>

by the prior art to be effective for the same purpose, that is the oncolysis of tumor cells and non-virulence to cells of the CNS."

This assertion of *prima facie* obviousness relies on the idea that the prior art shows HSV1716 to be effective in oncolysis of tumor cells (see the sections underlined above). This misconstrues the prior art. Roizman does not discuss HSV1716, this is the subject of Brown and MacLean and, as discussed, these references refer to neurovirulence *in vivo* in healthy mice. The effect of HSV1716 in tumor cells was not tested. The information regarding the efficacy of HSV1716 in tumor cells required by the examiner to substantiate the line of reasoning given above is simply not present in Brown and *prima facie* obviousness cannot be found.

It appears that the Examiner is applying properties of HSV1716, which are now known, but were not until the time of the invention, to the prior art. Clearly this is to use hindsight and is an impermissible approach.

Roizman, Brown and Martuza

One must first consider what the combination of Martuza and Roizman teaches.

Martuza takes the R3616 mutant of Roizman and alters it, by incorporating an additional (ribonucleotide reductase) mutation. Thus, any combination of these two references must involve that mutation. To combine the teachings and reach something excluding the ribonucleotide reductase mutation would not make sense.

Moreover, the experiments in Roizman are all performed *in vitro* and relate to primary neuronal tumor cells. The experiments in Martuza also only relate to primary tumors. The Examiner refers to treatment of melanoma cells, which per se are primary tumor cells, and extrapolates to say that treatment of melanoma derived secondary tumor cells is obvious. This is a gross simplification. Primary and secondary tumors can be completely distinct in their biochemistry and morphology and whilst the skilled person could hope that a treatment for the former would be effective for the latter one could never reasonably expect this to be the case.

At the paragraph bridging pages 9 and 10 of the Office action, the Examiner states:

> "Further, it would have been *prima facie* obvious and one would have been motivated to make the substitution in order to treat a cancer/tumorogenic disease, that is malignant melanoma, because US Patent No. 6,139,834 [Martuza] teaches the use of a replication-competent viral vector, preferably a herpes simplex virus, suitable for use in humans, that is capable of killing human tumor cells *in vivo*, including melanoma, that exhibits hypersensitivity to anti-viral agents and an inability to revert to wild-type virus, and that is not neurovirulent at a dose required to kill tumor cells and the HSV-1 mutant 1716 exhibits these properties."

Again, to say that Brown and/or Maclean show HSV1716 to kill human tumor cells *in vivo* goes beyond the teaching of the prior art. As discussed, this is not demonstrated in the prior art cited and, based on this, no *prima facie* obviousness can exist.

Martuza, Brown, Olofsson, Bolovan, MacLean

The Examiner has considered this combination at pages 6-7 of the Office action. The Examiner's conclusions appear to be based on the notion that Brown teaches that 1716 kills non-neuronal tumor cells by oncolysis. The reasoning being that 1716 retains the ability to replicate in peripheral tissues. This is set out on page 6, 1st paragraph of the Office action.

As previously discussed, this assertion is mis-founded. Replication and virulence are not equivalent things and one cannot conclude from Brown that 1716 kills non-neuronal tumor cells, or indeed any tumor cells.

Furthermore, the statement on page 7 that "... it would be expected that the 1716 construct would be virulent to intracranial rapidly dividing metastatic melanoma cells..." is mere speculation. Olofsson indicates that HSV-1 can infect melanoma cells and Bolovan **suggests** that the physiological state of the cell is an important factor in permissivity of HSV mutants, but that **further experimentation is required** (page 54 top of col. 2). MacLean is concerned with **growth** of HSV, but one must not confuse growth (and replication) with virulence.

Taking the information together and as a whole, a mental leap is required to go from the infection of **melanoma** cells by HSV, the virulence of certain HSV strain 17 mutants in

particular **non-tumor** dividing cells ***in vitro*** and the **replication** of HSV1716 in certain other dividing cells, to the conclusion that HSV1716 will selectively infect, replicate and lyse **secondary** tumor cells located in the CNS which are derived from primary melanoma cells.

Martuza/Roizman, Brown, Amer and Budman

The Examiner refers to this combination at page 7-8 of the Office action in reference to the motivation of the skilled person. Budman and Amer are relied upon to indicate the severe and often fatal nature of malignant melanoma and CNS metastases. That these conditions are severe and that treatments are sought is not disputed. However, the motivation to **try** and treat a particular tumor with the **hope** of succeeding should not be confused with reasonable expectation of success. Indeed, the inventors would not have undertaken their work if they did not **hope** to succeed.

Obviousness – general comment

The Examiner is reminded that the content of each prior art reference must be determined "at the time the invention was made" (MPEP 2141.01 III). To use hindsight in the analysis of the prior art and the invention is impermissible.

One must consider that at the time of the invention there was considerable uncertainty regarding the cause of the different infection, replication and virulence profiles of HSV mutants in different cells. There was also uncertainty as to whether results obtained in *in vitro* experiments could be applied *in vivo*.

In the present situation, the tumor type investigated by the inventors involved additional uncertainty owing to the fact that the tumor cells are amongst a non-native background cell population. The effect of the HSV mutants on the tumor cells relative to the surrounding cells, the characteristics of which may have been altered by the presence of the non-CNS derived tumor cells, was uncertain and unpredictable.

Referring back to the MPEP 2141 and 2142, Applicants submit that the references cited do not suggest the desirability and obviousness of making the contributions proposed by the

Examiner. Too many uncertainties arise in making the suggested combination of teachings and neither can one say that the prior art references teach or suggest all of the claim limitations or that the skilled person would have a reasonable expectation of success if they were to do so.

The inventors found that particular HSV mutants are effective in treating metastatic tumors occurring in the CNS. This outcome, on an objective assessment of the prior art, was not predictable with a reasonable expectation of success.

37 CFR §1.56 Duty of disclosure

The Examiner is made aware of co-pending US patent application 09/117,218 in the names of The Trustees of the University of Pennsylvania, The University Court of the University of Glasgow and The Wistar Institute.

The Examiner is also made aware of "Intralesional injection of herpes simplex virus 1716 in metastatic melanoma", Mackie *et al.*, *The Lancet*, Vol 357, February 17 2001, Pages 525-526 which is submitted herewith.

Conclusion

It is respectfully submitted that the present claims are in a condition for allowance.

If any issues remain, the Examiner is formally requested to contact the undersigned attorney prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. Applicants submit the foregoing Amendment so that the Examiner may fully evaluate Applicants' position, thereby enabling any such interview to be more focused.

This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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